American Journal of Medical Genetics 66:7–10 (1996)

Neurofibromatosis Type 1 and Pregnancy

Lorraine Dugoff and Eva Sujansky
Department of Obstetrics (L.D.) and Pediatrics (E.S.), University of Colorado Health Sciences Center, Denver

Neurofibromatosis Type 1 (NF-1) is an autosomal dominant condition which has markedly variable clinical expression, with manifestations ranging from mild cutaneous lesions to severe orthopedic complications and functional impairment. The current obstetrical literature indicates that women with NF-1 have increased complications associated with pregnancy. However, the majority of publications are case reports involving no more than 11 patients each, and are likely biased toward reporting on cases in which complications occurred.

This study presents data on pregnancy outcome in 105 women with NF-1. The data were obtained from questionnaires completed by the study participants, and by review of their pregnancy and peripartum medical records. The 105 women had a total of 247 pregnancies, resulting in 182 live births, 44 first trimester spontaneous abortions, 21 elective terminations, and 2 ectopic pregnancies. There were two sets of twins. The cesarean section rate in our series (36%) was greater than the general population rate (9.1–23.5%). In 7 of these patients, the cesarean section was required because of maternal NF-1 complications. The study did not show the previously reported increased incidence of preeclampsia, preterm delivery, intrauterine growth restriction, pregnancy-induced hypertension, stillbirth, spontaneous abortion, or perinatal mortality.

Sixty-four (60%) of the one hundred five women reported growth of new neurofibromas during pregnancy and fifty-five (52%) noted enlargement of existing neurofibromas. Nineteen women observed no changes in the size of their neurofibromas and no growth of new neurofibromas during pregnancy. © 1996 Wiley-Liss, Inc.

Received for publication July 24, 1995; revision received December 23, 1995.

Address reprint requests to Dr. Eva Sujansky, Director, Neurofibromatosis Clinic, University of Colorado Health Sciences Center/Children's Hospital, Box B300, 1056 East 19th Avenue, Denver, CO 80218.

KEY WORDS: pregnancy, neurofibromatosis, neurofibromatosis type 1, pregnancy complications

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is an autosomal dominant condition, occurring in approximately 1 out of every 4,000 births [Stumpf et al., 1987]. About 50% of cases of NF-1 result from de novo mutations. Penetrance is virtually 100% by the age of 5 years [Huson et al., 1989]. However, NF-1 has markedly variable clinical expressivity, which is both inter- and intrafamilial, with manifestations ranging from mild cutaneous lesions to severe orthopedic complications and functional impairment. Many authors have suggested that women with NF-1 have an increased frequency of pregnancy complications.

To date, only limited information is available on pregnancy in women with NF-1. Published case reports point to associations with intrauterine growth restriction [Blickstein and Lancet, 1987; Belton et al., 1984], eclampsia [Sherman and Schwartz, 1992], and oligohydramnios [Belton et al., 1984]. Other studies, which include a maximum of 11 patients each, have reported increased rates of preeclampsia [Sharma et al., 1991; Edwards et al., 1983], pregnancy-induced hypertension [Swapp and Main, 1973], preterm labor [Edwards et al., 1983], spontaneous abortion [Weissman et al., 1993], stillbirth [Weissman et al., 1993], and growth of neurofibromas with regression in size after delivery [Ansari and Nagamani, 1976]. Based on a single case report, Ansari and Nagamani [1976] recommended early termination of pregnancy and sterilization for women with NF-1 because of the deleterious effect of pregnancy on the course of disease, the poor pregnancy outcome, and the possibility of transmission to the fetus. Sharpe and Young [1936] reported on four women in whom pregnancy was associated with the first appearance of cafe au lait spots and neurofibromas. Although they concluded that there were no complications of delivery as a result of the disorder, they did advise preventing pregnancy in women with NF-1. They cited cosmetic effects as well as a potential for pain secondary to tumor encroachment on nerves, possibility of bone or central nervous system involvement, and the chance of ulceration or malignant degeneration as reasons to prevent pregnancy in women with NF-1,

TABLE I. Obstetric Complications in 105 Women With NF-1*

	Number	%	General population incidence[b] (%)
Preterm delivery	10	6	10
Preeclampsia	7	4	7
Intrauterine growth restriction	7	4	4-8
Pregnancy-induced hypertension	4	2	
Preterm premature rupture of membranes	3	2	1-4
Premature rupture of membranes	6	3	8-10
Abruptio placentae	1	0.6	0.8
Placenta accreta	1	0.6	
HELLP syndrome[a]	1	0.6	
Postpartum hemorrhage	6	3	
Cesarean section	65	36	9.1[c]-23.5[d]

* Number and % out of a total of 180 deliveries which resulted in 182 live births.
[a] Hemolysis, elevated liver enzymes, low platelets.
[b] Creasy and Resnik [1994].
[c] Shiono et al. [1987].
[d] Morbidity and Mortality Weekly Report [1993].

including the milder forms. In contrast, in a review of 27 pregnancies in 10 women with NF, Jarvis and Crompton [1978] did not observe any increased incidence of obstetric complications over the general population risk. Riccardi's observations [1992] are consistent with those of Jarvis and Crompton. He believes that no significant obstetric complications are likely to develop if there are no apparent problems prior to pregnancy, though he recommends that an NF-1 pregnancy be considered high risk and thus followed closely by an obstetrician who is aware of the problems which may be associated with NF-1.

In light of the minimal literature and conflicting reports on this topic, we decided to conduct a study on a larger sample of women with NF-1 who have experienced pregnancy. The general objectives of our study were to evaluate the rate of pregnancy complications in women with NF-1, the effect of pregnancy on the course of NF-1, and to evaluate neonatal morbidity.

MATERIALS AND METHODS

Women with NF-1 with at least one pregnancy were recruited through the Denver Neurofibromatosis Clinic for adults and children and via national neurofibromatosis newsletters. All of the women included in this study had a definite diagnosis of NF-1 according to the diagnostic criteria established at the 1987 National Institutes of Health Consensus Development Conference on Neurofibromatosis [Stumpf et al., 1987]. Patients who responded favorably were mailed a questionnaire and were asked to sign a form for release of medical records. Only those women who completed the questionnaire and for whom complete records of pregnancy and the peripartum period were available for review were included in this analysis. Thus, with the exception of growth of neurofibromas, which was subjectively reported, these data were derived from a review of patient medical records and not from the patient's recollections.

RESULTS

Complete data are available for 105 women with NF-1. Gravidity in the 105 women ranged from one to 10 pregnancies, with a mean of 2.3. Parity ranged from zero to 5 liveborn children, with a mean of 1.7. Twenty-nine of the women were residents of Colorado, while the remaining seventy-six women were from 29 different states. Twenty-six women were invited to participate in our study through the Denver NF clinic and 79 were recruited through local and national NF newsletters.

Pregnancy Complications in Women With NF-1

The 105 women had a total of 247 pregnancies. Twenty-one pregnancies were electively terminated. Forty-four pregnancies resulted in first trimester spontaneous abortion and two women had ectopic pregnancies. There were no stillbirths. The remaining 180 pregnancies resulted in 182 live births with two sets of twins. One-hundred and seventy-two newborns were delivered at term and there were 10 preterm deliveries. There were 10 cases of breech presentation at term, comprising 5.8% of term pregnancies.

Table I summarizes obstetric complications which were observed in the 180 pregnancies resulting in live births. There were no cases of eclampsia and none of the four women who were noted to have a history of chronic hypertension was diagnosed with superimposed preeclampsia.

The indications for cesarean section are listed in Table II. In seven of these cases, the cesarean section was performed as a direct result of maternal NF-1 com-

TABLE II. Indications for Cesarean Section (C/S) in Women With NF-1

Indication	Number	%
Cephalopelvic disproportion	24	37
Fetal distress	12	18
Malpresentation	12	18
Elective repeat	12	18
Severe preeclampsia at 26 weeks gestation	2	3
Abruptio placentae	1	2
Pheochromocytoma	1	2
Neurofibroma on spinal cord	1	2
Total C/S	65	100%

plications listed in Table III. The cases involving severe pelvic bony contractures resulted in arrest of descent disorders. Such bony contractures may include severe kyphoscoliosis of the lower spine or other pelvic bone abnormalities which may prevent descent of the fetal head into the pelvis. One of the women with pelvic neurofibromas was noted to have a large neurofibroma involving her left vulva and left vaginal wall which was felt to be obstructive. At the time of her scheduled cesarean section, she was noted to have a neurofibroma growing in the abdominal wall overlying the lower uterine segment, thus making the lower uterine segment inaccessible. Thus, she had an elective classical cesarean section performed at 36 weeks gestation, involving delivery through a vertical incision in the uterine fundus as opposed to a standard transverse incision in the lower uterine segment. The other two women were noted to have large neurofibromas protruding into the pelvis. In one case the fetus was in a breech presentation and in the other, the patient had an arrest of descent in the second stage of labor. She had a retroperitoneal pelvic tumor resected 10 months after delivery. The woman diagnosed with a pheochromocytoma at twenty-four weeks gestation was delivered at 36 weeks by an elective cesarean section which was then followed by an exploratory laparotomy and right adrenalectomy. The woman requiring early delivery by cesarean section secondary to the presence of a neurofibroma on her spinal cord underwent spinal surgery several weeks after delivery.

Reported NF-1 Changes During Pregnancy

Sixty-four (60%) of the one hundred five women reported growth of new cutaneous neurofibromas during pregnancy. Of these sixty-four women, six multiparous women experienced new growth with only selected pregnancies. NF-1 was first diagnosed in four women during pregnancy, as they noticed appearance of cutaneous neurofibromas for the first time.

Fifty-five (52%) of the one hundred five women reported enlargement of existing neurofibromas. Eighteen (33%) of these women noted a decrease in the size of their neurofibromas in the postpartum period. One woman terminated pregnancy at 6 weeks gestation secondary to growth of multiple new neurofibromas. These lesions did not decrease in size after she terminated her pregnancy. Nineteen (18%) of the one hundred five women observed no changes in the size of their cutaneous neurofibromas and no growth of new neurofibromas during pregnancy.

TABLE III. Maternal NF-1 Complications Resulting in Cesarean Section (C/S)

Maternal NF-1 complication	Number of C/S
Pelvic neurofibromas	3
Pelvic bony abnormality +/- kyphoscoliosis	2
Pheochromocytoma	1
Neurofibroma on spinal cord	1

Offspring

There were 182 offspring: 92 females and 90 males. The mean birthweight was 7 pounds and 7 ounces, with a range of 14 ounces to 10 pounds and 10 ounces. No neonatal deaths occurred. At the time of our study, 76 offspring have been diagnosed with NF-1, 41 have not shown signs of NF-1 on physical examination, and 65 have not yet been evaluated.

DISCUSSION

Due to the controversial and limited information available, we conducted a study of pregnancy in women with NF-1 involving over 100 women. We attempted to recruit patients in a non-biased manner. We recognize that women recruited through the NF newsletters may have been more likely to respond if they had pregnancy complications. The 26 women ascertained through the Denver NF clinic were followed routinely in the clinic prior to the initiation of the study. None of these women came to the clinic because of issues relating to pregnancy complications. Virtually all women seen in the Denver NF clinic agreed to participate in our study. If ascertainment bias affected our results, it would likely increase the rate of complications. Though we did not stratify the women in our study by the severity of their NF-1 complications, the majority of women did not have severe manifestations of NF-1. Most of the women had cafe-au-lait spots and neurofibromas with no additional manifestations.

As seen in Table I, 180 viable pregnancies in 105 women with NF-1 were not associated with an increased incidence of preeclampsia, preterm delivery, intrauterine growth restriction, pregnancy-induced hypertension, stillbirth, spontaneous abortion or perinatal mortality, as previously had been found in the literature. The only obstetrical complication observed to occur with increased frequency was cesarean section delivery.

The rate of delivery by cesarean section in the general population in the United States ranges from 9.1% in 1974 [Shiono et al., 1987] to 23.5% in 1991 [Morbidity and Mortality Weekly Report, 1993]. Despite the fact that we found an increased rate of cesarean section in our series (36.1%), the incidence of elective repeat cesarean section (18%) was considerably lower than the 1991 national average of 35% [Morbidity and Mortality Weekly Report, 1993]. In seven of our cases, the cesarean section was performed because of sequelae of NF-1, including severe pelvic bone contractures and pelvic neurofibromas. The increased rate of cesarean section may be partially attributable to an increased incidence of malpresentation and cephalopelvic disproportion. While we observed cesarean section associated with malpresentation and cephalopelvic disproportion at rates of 18% and 37%, respectively, in 1991 in unaffected women cesarean section was performed for malpresentation in 11.7% of cases and for dystocia in 30.4% of cases [Morbidity and Mortality Weekly Report, 1993]. We speculate that some of the cases of malpresentation and cephalopelvic disproportion in our series might have been the result of undiagnosed pelvic (possibly retroperitoneal) neurofibromas and pelvic con-

tractures, including cases of kyphoscoliosis affecting the lower spine. Other possible causes of malpresentation could be hypotonia and/or macrocephaly, more frequently observed in infants with NF-1 [Brill, 1989]. Fetal macrocephaly, if present, could also explain an increased incidence of cephalopelvic disproportion. Since 65 of the offspring have not been evaluated for NF-1 and many of those not diagnosed early in life could be found to have NF-1 later, we could not analyze the cesarean section rate for infants with NF-1 versus those without NF-1.

With respect to NF-1 changes during pregnancy, 80% of women in our study reported either appearance of new or growth of existing neurofibromas or both, indicating that pregnancy may promote neurofibroma growth. Since these data were derived from subjective retrospective reporting by the study participants, the accuracy may be questioned. Even if the reporting is reliable, in the absence of a control group, it is not clear how much of this increased growth can be attributed to the hormonal changes associated with pregnancy as opposed to the natural progression of the disease. However, the reported initial appearance of neurofibromas during pregnancy, regression of some neurofibromas immediately following pregnancy, and the presence of estrogen receptors in selected neurofibromas in some women [Leslie et al., 1992] support the notion that this growth is not purely coincidental. Clearly this issue deserves further investigation, optimally utilizing a prospective study design.

Our study indicates that common obstetrical complications are not more frequent in women with NF-1 than in the general population, but there may be a subgroup of women with NF-1 who may be at increased risk for obstetrical complications and may require close surveillance at a high-risk obstetric center. The presence and degree of kyphoscoliosis, pelvic bony abnormalities and pelvic neurofibromas should be noted as they may cause dystocia or malpresentation, necessitating a cesarean delivery. In the future, it would be helpful to conduct a prospective study involving a national collaborative effort to evaluate pregnancy outcome in women with NF-1, with correlation of the findings with the degree of severity of the disorder.

REFERENCES

Ansari AH, Nagamani M (1976): Pregnancy and neurofibromatosis (von Recklinghausen's Disease). Obstet Gynecol 47:9s–25s.

Belton SR, Ferguson JE, Catanzarite VA (1984): Neurofibromatosis and pregnancy: Report of a case complicated by intrauterine growth retardation and oligohydramnios. Am J Obstet Gynecol 149:468–469.

Blickstein I, Lancet M (1987): Fetal growth retardation as a complication of pregnancy in patients with neurofibromatosis. Am J Obstet Gynecol 157:343.

Brill CB (1989): Neurofibromatosis: Clinical overview. Clin Orthop 245:10–15.

Creasy RK, Resnik R (1994) "Maternal Fetal Medicine: Principles and Practice." Philadelphia: W.B. Saunders, pp 494, 560, 610, 625, 807.

Edwards JN, Foohs M, Davey DA (1983): Neurofibromatosis and severe hypertension in pregnancy. Br J Obstet Gynaecol 90:528–531.

Huson SM, Compston DAS, Clark P, Harper, PS (1983): A genetic study of Von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 26:704–711.

Jarvis GJ, Crompton AC (1978): Neurofibromatosis and pregnancy. Br J Obstet Gynaecol 85:844–846.

Leslie KK, White M, Sujansky E (1992): Utilization of polymerase chain reaction (PCR) for identification of estrogen receptors in neurofibromas: Potential clinical significance [Abstract]. National Neurofibromatosis Foundation Annual Clinical Care Conference.

Rates of cesarean delivery—United States (1993): Morbidity and Mortality Weekly Report 42:285–289.

Riccardi VM (1992): "Neurofibromatosis: Phenotype, Natural History and Pathogenesis." Baltimore: Johns Hopkins University Press, pp 139–141.

Sharma JB, Gulatri N, Malik S (1991): Maternal and perinatal complications in neurofibromatosis during pregnancy. Int J Gynecol Obstet 34:221–227.

Sharpe JC, Young RH (1936): Neurofibromatosis: the effect of pregnancy on the skin manifestations. JAMA 106:682–683.

Sherman SJ, Schwartz DB (1992): Eclampsia complicating a pregnancy with neurofibromatosis: A case report. J Repro Med 37: 469–472.

Shiono PH, McNellis D, Rhoads GG (1987): Reasons for the rising cesarean delivery rates; 1978–1984. Obstet Gynecol 69:696–700.

Stumpf DA, Alksne JF, Annegers JF (1987): Neurofibromatosis. NIH Consensus Development Conference Statement, vol. 6, no. 12. Washington, DC, US Government Printing Office (also published in Arch Neurol 45:575, 1988).

Swapp GH, Main RA (1973): Neurofibromatosis in pregnancy. Br J Dermatol 80:431–434.

Weissman A, Jakobi P, Zaidise I, Drugan, A (1993): Neurofibromatosis and pregnancy: An update. J Repro Med 38:890–896.